DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING

MAY 3, 1985

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RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING[1]

MAY 3, 1985

The Recombinant DNA Advisory Committee (RAC) was convened for its thirty-second meeting at 9:00 a.m. on May 3, 1985, in Building 31, Conference Room 6, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20205. Mr. Robert Mitchell (Chair), Attorney at Law in California, presided. In accordance with Public Law 92-463, the meeting was open to the public. The following were present for all or part of the meeting:

Committee members:

Royston Clowes
Mitchell Cohen
L. Albert Daloz
Bernard Davis
David Friedman
Susan Gottesman
Irving Johnson
Wolfgang Joklik
Arthur Landy
David Martin
Mark Mills
Robert Mitchell
Thomas Pirone
David Pramer
Fred Rapp
Mark Saginor
Frances Sharples
Anne Vidaver
LeRoy Walters
Pieter Wensink
Anne Witherby
William J. Gartland, Jr. (Executive Secretary)

A committee roster is attached (Attachment I).

Ad hoc consultant:

Gerard McGarrity, Institute for Medical Research

Non-voting members:

William Beisel, Department of Defense
George Duda, Department of Energy
John R. Fowle, Environmental Protection Agency
Philip D. Harriman, National Science Foundation
Morris A. Levin, Environmental Protection Agency
Henry I. Miller, Food and Drug Administration
Edwin Shykind, Department of Commerce
Sue A. Tolin, Department of Agriculture
William J. Walsh, Department of State

[1]The RAC is advisory to the NIH, and its recommendations should not be considered as final or accepted. The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

National Institutes of Health staff:

Stanley Barban, NIAID
Bobbie Bennett, OD
Robert Bonner, OD
Thomas Cloutier, OD
Becky Connors, NIAID
Irving Delappe, NIAID
Rosalind Gray, OD
Caroline Holloway, OD
Tateo Icho, NIADDK
Rachel Levinson, OD
Grace McDonald, OD
Robert McKinney, OD
Elizabeth Milewski, NIAID
Donald Ralbovsky, OD
Clifford C. Scharke, OD
Bernard Talbot, NIAID

Others:

Stanley H. Abramson, Environmental Protection Agency
Karen A. April, BioTechnica International, Inc.
Amy Bain, Lederle Laboratories
Frederick S. Betz, Environmental Protection Agency
Irene Brandt, Eli Lilly and Company
Steven Budiansky, Nature Magazine
Kathleen Canter, CBS Radio
Chia Ting Chen, Department of Labor
James F. Childress, Wilson Center, Smithsonian Institution
Isabelle Davidson, Pfizer, Inc.
Theodore J. DeLoggio, Pennwalt Corporation
Dominic D. Diascro, Jr., Pennwalt Corporation
Marie A. Dray, Pharmaceutical Manufacturers Association
Paula Dwyer, McGraw-Hill
Charles J. Eby, Monsanto Company
Neal Farber, Biogen Research Corporation
Peter Farnham, American Society for Biological Chemists
Gershon W. Fishbein, Environews, Inc.
Jeffrey Fox
Robert J. Frederick, Environmental Protection Agency
Luther Val Giddings, Office of Technology Assessment, U.S. Congress
Alan Goldhammer, Industrial Biotechnology Association
Carol Lax Gronbeck, Genentech, Inc.
Marlin Harmon, National Food Processors Association
Judith A. Hautala, Genex Corporation
Anne Hollander, Environmental Protection Agency
Don Irwin, LA Times
Susan James, NOVA
Dorothy Jessop, Department of Agriculture
Judy Johnson, Congressional Research Service

Roger S. Johnson
Geoffrey M. Kamy, Finnegan, Henderson, Farabow, Garrett, and Dunner
John H. Keene, Abbott Laboratories
Martin Kenney, Ohio State University
Lorraine Kershner, Office of Assistant Secretary for Health, DHHS
Rihito Kimura, Kennedy Institute
Dennis Kopecko, Walter Reed Army Medical Center
Patrice Laget, French Embassy
Althaea Langston, Department of Agriculture
Robert Lanman, Office of General Counsel, DHHS
Warren Leary, Associated Press
Steven Lyons, Environmental Protection Agency
Kathryn R. Mahaffey, National Institute for Occupational Safety and Health
Jack J. Manis, Upjohn Company
Carl Mazza, Environmental Protection Agency
Julie Miller, Science News
Lorraine C. Minecci, Wyeth Laboratories
James Moe, Walter Reed Army Medical Center
David Moore, Association of American Medical Colleges
Claire Nader
Steve Olson, National Academy of Sciences
Vladimir Pakhomov, USSR Embassy
Sandra Panem, Environmental Protection Agency
Thomas L. Parker, Genetics Institute
Tabitha Powledge, Institute for Scientific Information
James Peterson, University of Virginia
Eleanor H. Peckham, Blum, Nash, and Railsback
Ronald A. Rader, Biotechnology Information Institute
Jeremy Rifkin, Foundation on Economic Trends
Patricia Roberts, Environmental Protection Agency
Marvin Rogul, The Rogul Group
Ronald L. Schaefer, ECOsystems International, Inc.
Harold Schmeck, New York Times
Mark C. Segal, Environmental Protection Agency
Smita K. Siddhanti, University of Pittsburgh
George P. Shibley, Department of Agriculture
Janet Shoemaker, American Society for Microbiology
William R. Srigley, Invitron
Paul E. Stern, University of Florida
Clarence E. Styron, Monsanto Company
Marjorie Sun, Science Magazine
Laura Tangley, Bioscience
Susan Thompson, Food and Drug Administration
Charles Turbyville, NIH Week
Joseph Van Houten, Schering-Plough
Vitolis E. Vengris, Food and Drug Administration
Lidia Watrud, Monsanto Company
Charles Weiner, Massachusetts Institute of Technology
Patricia Williams, Blue Sheet
Judith Wortman, American Institute of Biological Sciences
Stephanie Zobrist, Embassy of Switzerland

I. CALL TO ORDER AND OPENING REMARKS

Mr. Mitchell, Chair, called the meeting of the Recombinant DNA Advisory Committee (RAC) to order. He said notice of this formal public meeting had been given in the March 28, 1985, Federal Register (50 FR 12456). He asked Dr. Gartland, Executive Secretary, whether a quorum was present. Dr. Gartland said a quorum was present.

Mr. Mitchell said in order to move expeditiously on a full agenda, he would recognize individuals in the following order: primary reviewers; other RAC members; ad hoc consultants to RAC; non-voting representatives to the RAC; RAC's administrative staff; members of the public who submitted written documents or comments; and finally other members of the public who wish to comment.

Mr. Mitchell welcomed several new committee members: Dr. Anne Vidaver of the University of Nebraska; Dr. Bernard Davis of Harvard University; Dr. David Pramer, of the Waksman Institute of Microbiology, Rutgers University; Dr. Mitchell Cohen of the Centers for Disease Control; and Dr. Irving Johnson of Eli Lilly and Company.

II. MINUTES OF THE OCTOBER 29, 1984, MEETING

Mr. Daloz said he and Dr. Saginor found the minutes (tab 1209) of the October 29, 1984, meeting of the RAC to be correct. He said that questions posed by the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services (DHHS), had been well answered by the RAC Risk Assessment Subcommittee.

Dr. Saginor said the minutes were as lively to read as he remembered the meeting.

Dr. Gottesman moved approval of the minutes. The motion was seconded.

By a vote of twenty in favor, none opposed, and no abstentions, the RAC accepted the minutes of the October 29, 1984, RAC meeting.

III. REPORT OF THE WORKING GROUP ON RELEASE INTO THE ENVIRONMENT

Dr. McGarrity of the Institute for Medical Research, the Chair of the RAC Working Group on Release into the Environment, said he had made a preliminary report at the October 29, 1984, RAC meeting on the attempt of the Working Group on Release into the Environment to develop a points to consider document for field testing modified microorganisms (tabs 1202, 1203, 1204, 1216, 1217, 1218, 1219, 1227).

Dr. McGarrity said the working group's objectives were: (1) to develop submission guidance for investigators wishing to test microorganisms modified through recombinant DNA in the field; and (2) to facilitate RAC review.

Dr. McGarrity said the points to consider document begins with a general introduction to the topic of environmental testing. The first section of the document requests investigators to provide a general summary, to describe the objective(s) and the significance of the proposal, and to justify the proposal. The second section of the document requests information on the non-modified parental organism as well as information on the construction and molecular biology of the modified organism. The third section of the document requests information on environmental and ecological considerations. The fourth section of the document requests information on the conditions of the proposed field trial. The fifth section asks the investigator to provide a risk analysis.

Dr. McGarrity emphasized that the points to consider are general guideposts. Some of the points may not need to be addressed in a particular application; on the other hand, more information than requested by the points to consider may be required for some applications. Review of applications would be performed on a case-by-case basis.

Dr. McGarrity said these points to consider are not submitted for inclusion in the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules. The points to consider are intended to serve as guidance for investigators; these points should be flexible and modified as data accumulate from the testing continuum which extends from laboratory bench, to growth chamber or greenhouse, and to small-scale field testing.

Dr. Talbot, Deputy Director of the National Institute of Allergy and Infectious Diseases, said neither a vote by the RAC nor acceptance by the NIH Director is required for points to consider documents; RAC might, therefore, simply note this document as the current thinking of the RAC. The document could then be sent to individuals requesting it.

Dr. McGarrity said he would prefer to have RAC's administrative approval of the document.

Mr. Mitchell asked how a flexible oversight system could be developed with the great diversity of organisms, test sites, and techniques which could be used in field testing. Dr. Gottesman replied review must be performed on a case-by-case basis because of this great diversity.

Dr. Gottesman said comment letters (tabs 1216, 1227) had been received on the points to consider document in response to the March 28, 1985, Federal Register announcement. She suggested these comments be considered by the working group at its next meeting. Dr. Pirone said the issues raised in these comment letters could be handled rather simply by the working group

since the group has already discussed many of these points in detail. Dr. Vidaver agreed most of the points raised in the comment letters were considered by the working group in its extensive discussions.

Dr. Sharples said the points to consider document represents important compromises between a great diversity of opinion. She suggested the working group and RAC not introduce major changes in the document until the points to consider have been used to evaluate an actual field trial.

Dr. Johnson said he supported the points to consider document but suggested that in the future consideration be given to whether certain "innocuous" modified organisms could be exempted from review like "self-cloning experiments" in the laboratory.

Dr. Gottesman said the working group had discussed this possibility but could only agree that "information on all these points will not be necessary in all cases." She felt, however, the working group could perhaps attempt to distinguish cases which would not necessarily be exempt but which would not require a great deal of information for review. Dr. Gottesman said this approach would be in keeping with the manner in which the NIH Guidelines have evolved. Originally all experiments were covered by the NIH Guidelines. As information became available, requirements for some categories of experiments were reduced, and some categories of experiments were eventually exempted from review.

Dr. McGarrity reemphasized that modifications would be introduced into the points to consider document as data and experience accumulate. He expressed concern that this type of flexibility might not be present in oversight mechanisms proposed by other government agencies.

Dr. Pirone said although certain microorganisms in their natural state are innocuous, they may not be innocuous when altered. The interactions of microorganisms in nature are not well documented, and caution is appropriate.

Dr. Landy said he in principle supported attempts to develop categories of exempt organisms. However, no control would be applied over how exempt organisms would be introduced into the environment. Although a modified organism may be a variant of one occurring in nature, an investigator might disperse it in ways not normal in nature. While there may be no long-term environmental impact from such procedures, the possibility of transient effects should also be considered at this time. The working group approach is appropriate, and the document is currently an excellent guide for evaluating testing of modified microorganisms in the environment.

Dr. Clowes said the points to consider document represents a compromise between views of microbiologists and ecologists. Although some working group members felt some of the information requests were onerous and unnecessary, the correct approach clearly is to construct a flexible document to which individuals can respond as appropriate.

Dr. Gottesman said the working group expects the investigator to determine which points are important in the particular proposal and to provide relevant information to the working group and the RAC.

Dr. Davis said less information should be required for review if the modified organism is identical or virtually identical to something found in nature. He did not think RAC should develop a review system requiring a great deal of paperwork simply to relieve public anxiety over safe experiments.

Dr. Landy said RAC's attention to public concerns and anxiety has proven very beneficial; it is easier for RAC to modify its position than it is to reverse a court decision or legislation. Dr. Davis questioned whether widespread public concern actually exists or whether there is only a very vigorously expressed minority opinion.

Dr. Rapp supported Dr. Landy's comment; in order to build public confidence, RAC should proceed slowly and err on the side of caution so that the public feels environmental testing of modified organisms is being carefully monitored. As experience and information accumulate, RAC might consider creating exempt categories.

Dr. Gottesman said the distinction between the method of producing an organism and the product should not be lost: because an organism is produced using recombinant DNA techniques does not necesarily make it different from organisms derived by other means. A second issue is how environmental releases of any organism should be handled. Dr. Gottesman said: "...we run the danger of trying to solve every ecological problem in the world in the name of recombinant DNA and in most cases that is not really what the issue is."

Dr. Gottesman reminded the assembly that most genetic engineering using classical techniques and most transport of organisms from one location to another within the United States are not regulated.

Dr. Landy cautioned RAC to avoid situations which might unnecessarily impede recombinant DNA research. The public's perception of an issue is as important as the reality. If negative publicity is associated with transfer of an organism from one location to another, regardless of whether recombinant DNA is involved, that negative publicity may spill over to recombinant DNA research.

Dr. Gottesman thought RAC should begin to think about how to educate the public about these issues. She suggested RAC's discussion and the points to consider should serve as the basis for future considerations of environmental testing proposals. The points to consider document will evolve as experience accumulates.

Dr. Davis said about a dozen bacteria are now sold commercially for agricultural and other purposes. He agreed RAC should proceed cautiously but was concerned RAC might overreact to a perception of public concern and subject modified organisms, no more potentially harmful than those now on the

market, to an elaborate review process. He suggested organisms currently distributed commercially might be models for types of organisms to be considered for the exempt category.

Dr. Sharples said the Environmental Protection Agency (EPA) review process prior to approval of commercially available microbial pesticides is much more stringent than the process suggested in the RAC working group points to consider document. Mr. Fred Betz of the EPA corroborated Dr. Sharples' statement. He said: "EPA registration requirements are comprehensive in the area of product identity, human health considerations, environmental transport, and ecological effects." Historically, EPA has primarily reviewed large-scale experimental testing but recently has begun to evaluate microbial pesticides at the small-scale field testing stage.

Mr. Jeremy Rifkin of the Foundation on Economic Trends asked whether the recent decision (tab 1225) of the United States Court of Appeals for the District of Columbia Circuit had been addressed by the working group in developing the points to consider document. In developing the document did the working group address the issue of the adequacy of NIH environmental assessments.

Dr. McGarrity said the points to consider document is not designed to be an environmental assessment. In developing the points to consider, the working group considered many environmental concerns. The document represents the best scientific effort of this group of molecular biologists and environmental scientists.

Dr. Walters moved that RAC accept with thanks the points to consider document developed by the Working Group on Release into the Environment and request that in the future the working group submit to RAC any proposed major changes. Dr. Wensink seconded the motion.

By a vote of twenty in favor, none opposed, and no abstentions, the RAC accepted the motion.

Mr. Mitchell thanked Dr. McGarrity and the Working Group on Release into the Environment for an outstanding job. Dr. McGarrity thanked the EPA and the U.S. Department of Agriculture (USDA) for their significant contributions to this effort.

[Executive Secretary's Note: The document "Points to Consider for Environmental Testing of Microorganisms" is appended to these minutes as Attachment II.]

IV. PROPOSED REVISION OF APPENDIX C

Dr. Clowes introduced the proposal (tabs 1220, 1221) of Dr. Jack Manis of the Upjohn Company, Kalamazoo, Michigan. Dr. Manis had proposed that certain types of experiments involving Streptomyces fradiae and Streptomyces

lincolnensis be exempted under Section III-D-5 of the NIH Guidelines. The following language was proposed for inclusion in Appendix C of the NIH Guidelines:

"Experiments and processes utilizing recombinant DNA containing derivatives of Streptomyces fradiae or Streptomyces lincolnensis are exempt from the Guidelines at all levels of volume scale when the recombinant DNA molecules contained in these hosts are derived solely from nonpathogenic streptomycetes. The nonpathogenicities of the recombinant DNA sources are determined by the local Institutional Biosafety Committee (IBC).

"For these exempt laboratory experiments, BL1 physical containment conditions are recommended.

"For large-scale fermentation experiments BL1-LS physical containment conditions are recommended. However, following review by the IBC of appropriate data for a particular host-vector system some latitude in the application of BL1-LS requirements as outlined in Appendix K-II-A through K-II-F is permitted.

"Exceptions.

"Experiments described in Section III-A which require specific RAC review and NIH approval before initiation of the experiment.

"Experiments involving Class 3, 4, or 5 organisms (1) or cells known to be infected with these agents may be conducted under containment conditions specified in Section III-B-2 with prior IBC review and approval.

"Large-scale experiments (e.g., more than 10 liters of culture) require prior IBC review and approval (see Section III-B-5).

"Experiments involving the deliberate cloning of genes coding for the biosynthesis of molecules toxic for vertebrates (see Appendix F)."

Dr. Clowes said a previous broader request by Dr. Manis had been rejected by the RAC at the February 6, 1984, meeting because sufficient background information had not been supplied. Dr. Manis has now limited his request and provided relevant information. The request cites the taxonomic relationships between these two Streptomyces strains and other Streptomyces strains and indicates there are only two pathogens in this genus; Streptomyces somaliensis which produces fungal-like infections in humans and animals, and Streptomyces scabies which produces a scab-like disease on potatoes and sugar beets.

Dr. Clowes found Dr. Manis' arguments persuasive. He said Streptomyces lincolnensis and Streptomyces fradiae have been used for more than twenty years in large-scale antibiotic preparation. Although Streptomyces lincolnensis and Streptomyces fradiae strains have not been cultivated for

as long a period or on as large a scale as Saccharomyces cerevisiae, they have, nevertheless, been cultivated at the greater than 100,000 liter scale for decades without any evidence of negative effects. Moreover, the experiments for which exemption is requested would involve recombinant DNA only from demonstrated non-pathogenic strains of other Streptomyces.

Dr. Clowes said he was reluctant at this time to move approval of Dr. Manis' request, however, because he would like to question Streptomyces experts on the interrelationships of the various Streptomyces species. There appears to be some contradiction between the data supplied by Dr. Manis and the positions of various Streptomyces species on Appendix A of the NIH Guidelines. He suggested Dr. Manis' request be referred to the Large-Scale Review Working Group for further study.

Dr. Pramer supported Dr. Clowes' suggestion to obtain additional information from experts on Streptomyces. Dr. Wensink agreed.

Dr. Friedman asked to be excused from the discussion as he has collaborative arrangements with investigators at Upjohn Company. Dr. Gottesman asked Dr. Friedman to contribute his expertise and knowledge to the discussion; he would not, however, vote.

Dr. Manis said Upjohn Company was requesting criteria for exemption, other than genetic exchange, for organisms traditionally used in large-scale experimentation in developing commercially usable novel antibiotics. He suggested nonpathogenicity might be a criterion. Dr. Manis said he hoped by this means to simplify review requirements.

Dr. Davis said the taxonomic criteria defining the Streptomyces are so "fuzzy" that relationships between species may be close by one set of criteria but distant by another set. He said he would consider nonpathogenicity a fundamental criterion. Safe cultivation of an organism on the 100,000 liter scale for a decade provides more than sufficient evidence of nonpathogenicity.

Dr. Henry Miller of the Food and Drug Administration (FDA) said FDA has a great deal of experience overseeing commercial uses of Streptomyces. He said FDA scientists have reviewed the proposal, and on theoretical and experiential grounds urge approval. He added that "the decision has the specific approval of Frank Young, the FDA Commissioner, who is a former RAC member and a microbiologist."

Dr. Johnson said the British Genetic Manipulation Advisory Group (GMAG) excluded all non-pathogenic strains of Streptomyces five years ago. GMAG in essence considered manipulations involving nonpathogenic Streptomyces self-cloning experiments. He thought the Upjohn proposal requested an action more limited in scope than the GMAG action, and he suggested the proposal be approved.

Dr. Gottesman said the current NIH Guidelines permit these experiments at the laboratory scale at Biosafety Level 1 and specify that investigators

must notify their IBC simultaneously with initiation of these experiments. At the large-scale level, IBC approval must be obtained before initiation of the procedure. Dr. Manis' request, therefore, deals primarily with the issue of whether investigators must consult their IBC before they initiate these types of large-scale processes. Dr. Gottesman expressed discomfort with a request to approve a blanket exemption for these organisms.

Dr. Gottesman said she had several questions on the Streptomyces. For example, what is known about the mechanism of pathogenicity? What might influence the behavior of nonpathogens? What is the frequency of genetic transfer? Is there any ecological concern about introducing novel antibiotic synthetic ability into an organism? She thought discussions with Streptomyces experts would be useful.

Dr. Manis said he had been unable to demonstrate genetic exchange with Streptomyces lincolnensis or Streptomyces fradiae or between those two strains.

Dr. Davis asked whether Streptomyces lincolnensis and Streptomyces fradiae could be placed on a sublist of Appendix A of the NIH Guidelines.

Dr. Gottesman said organisms are added to Appendix A when data demonstrate genetic exchange between the organisms. If the organisms exchange genetic material in the laboratory, such exchange is assumed to occur in nature. No genetic exchange has been shown with Streptomyces lincolnensis and Streptomyces fradiae, however, so they cannot be included on Appendix A.

Dr. Friedman said he saw no reason to change the current NIH Guidelines which require IBC approval before scale-up of such experiments.

Dr. Manis said Upjohn Company was requesting the flexibility in determining large-scale containment procedures accorded E. coli and S. cerevisiae host-vector systems be accorded to procedures involving Streptomyces lincolnensis and Streptomyces fradiae.

Dr. Robert McKinney of the NIH Division of Safety, the Chair of the RAC Large-Scale Review Working Group, said the NIH Guidelines provide sufficient flexibility to proceed at the large-scale level.

Dr. Gottesman said Dr. Manis' request should be referred to the Large-Scale Review Working Group for consideration.

Mr. Van Houghton, the Chair of Schering Corporation's Institutional Biosafety Committee (IBC), supported the opinion that these cases should be evaluated by the IBCs.

No motion was offered on the proposal, and Mr. Mitchell suggested RAC proceed to the next agenda item.

V. PROPOSED RAC WORKING GROUP

Dr. Martin introduced the proposal (tabs 1206, 1207, 1210) by Mr. Lee Rogers, Attorney for the Foundation on Economic Trends, and Mr. Jeremy Rifkin to create a RAC working group "whose stated purpose would be to examine potential uses of recombinant DNA technology for offensive and defensive biological weapons systems. In addition, this working group would explore current Department of Defense (DOD) programs specifically designed to develop 'defensive' preparedness against the threat of genetic engineering warfare by aggressor nations or terrorists....The working group may also wish to make recommendations regarding future oversight of recombinant DNA work in this field."

Dr. Martin said Mr. Rogers and Mr. Rifkin offer several justifications for creating this working group. One is that:

> "It is no longer possible to ignore the potential military uses of recombinant DNA experimentation in light of the DOD's plan to construct an aerosol test laboratory at Dugway Proving Ground in Utah."

A second is that:

> "The only area of recombinant DNA experimentation that has not yet been rigorously examined is the potential military uses.... this committee would find it helpful to explore the potential military uses of recombinant DNA technology in order to facilitate a better understanding of the various issues involved. Moreover, it is altogether appropriate for the RAC to engage in such a study as the DOD has stated on many occasions that it is adhering to the guidelines established by this committee and the NIH. An independent study by the RAC of the military potential of recombinant DNA technology can only serve to better inform the Executive Branch, Congress and the public of the issues involved in this particular field."

Dr. Martin said recombinant DNA technology can be used to obtain valuable information about biological processes; this knowledge could lead to the ability to alter these processes. The potential usefulness of recombinant DNA technology for biological warfare is, thus, comparable to its usefulness in human and animal health and in producing commodity chemicals and does not differ from other technologies in potential for warfare applications.

Dr. Martin said Secretary of Defense Weinberger's letter (tab 1206) to Congressman Sasser states the U.S. remains committed to the 1972 Convention on the Prohibition of Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. He said a RAC working group would not be successful in obtaining non-public information from DOD. The executive and legislative branches have greater access to U.S. military recombinant DNA activities than does RAC. If these branches have questions concerning potential military use, RAC would be most willing to provide appropriate scientific expertise to evaluate these activities.

Dr. Martin said RAC has only formed working groups to examine areas where proposals have or will be submitted. There is no justification for forming a RAC working group to study potential military uses of recombinant DNA technology. RAC in the foreseeable future will not receive proposals involving the use of recombinant DNA technology in biological warfare.

Dr. Martin said:

> "What should RAC as a committee do? Nothing. What should we as individual scientists and citizens do? I consider that to be a matter that best be discussed before professional societies, a suggestion which the Foundation might note."

Dr. Walters suggested some RAC members might write as private citizens to Congress and request this issue be addressed.

Dr. Rapp said it is very difficult to verify that a biological system is being used for warfare; these difficulties are exemplified by the yellow rain issue in Southeast Asia.

Dr. Rapp said if one accepts DOD statements on its research programs, there is no need to explore this area; if one does not accept DOD statements, RAC is in no position to explore this area. RAC has neither the mandate, the resources, nor the budget to investigate these issues. He said he could not recommend RAC become involved in such an activity.

Dr. Gottesman said since the Asilomar Conference it has been recognized that this technology could be misused as well as applied to positive goals. This recognition is reflected in the structure of the NIH Guidelines which currently specifically require RAC review and NIH approval of certain types of proposals.

Dr. Gottesman said the question is whether RAC could do more to lessen the possibility this technology might be used for biological warfare. She thought RAC could do nothing more as a committee other than occasionally discuss this issue.

Dr. Davis said:

> "I'm as opposed to biological warfare as Mr. Rifkin and probably as suspicious of some aspects of military policy and I'm also aware of the fact that research for defensive purposes can be hardly distinguished from research that could conceivably someday contribute to offensive purposes...But I thoroughly agree...that this committee has no possible basis for trying to do anything useful in this field."

Mr. Rifkin said several recent developments should be considered by RAC. The Secretary of Defense went to Congress in August 1984 with an emergency request for funds to build a biological warfare aerosol test laboratory at Dugway Proving Grounds. Mr. Rifkin said the DOD Secretary indicated the

U.S. continues to obtain evidence the Soviet Union has maintained its offensive biological warfare program.

Mr. Rifkin said he had learned, but had not substantiated, that the Central Intelligence Agency (CIA) has been holding classified briefings for various agencies. At those briefings, the CIA is warning of a Soviet "threat" in genetic engineering. Mr. Rifkin said the chairman of a university molecular biology department had told him the CIA has been contacting molecular biologists to develop think-tank scenarios of possible uses of recombinant DNA technology in biological warfare.

Mr. Rifkin said the Department of the Army is using recombinant DNA technology in a cobra venom study. Several months ago several periodicals pointed out, but have not substantiated, that the Soviet Union was using recombinant DNA technology in research involving cobra venom. Mr. Rifkin said the DOD has received NIH permission to pursue this project; he asked RAC what is the redeeming social value of cobra venom research? He said: "Are there millions of people who potentially can be bitten by cobras around the world and therefore we need some kind of vaccine in order to inoculate them?"

Mr. Rifkin said RAC has examined every recombinant DNA technology application except biological warfare. He said RAC is "shirking" its responsibilities by not examining the ethics of using recombinant DNA technology in biological warfare.

Mr. Rifkin said he was suggesting RAC set up a working group to examine the technology and pose questions about the convertibility of this technology to biological warfare or military purposes. Such a mandate would not require investigation of DOD. Rather the working group would develop useful criteria to inform the public about the biological warfare implications of recombinant DNA technology. Mr. Rifkin said:

> "What has caused you in your collective minds to be so certain that there's absolutely no need for any other agency beside the Department of Defense to deal with the overall implications of recombinant DNA in this field. I just don't understand it and I'm really getting very frustrated and tired year after year of stone-walling and unanimous votes saying this committee has nothing to do with this technology because sooner or later you're going to have to deal with it. Sooner or later there's going to be a problem that's going to cause the Department of Defense to lock horns or the CIA or other agencies with this committee."

Mr. Mitchell said the United States has ratified the 1972 Biological Weapons Convention and RAC should not engage in any activity which might suggest the U.S. may be violating a treaty or is interested in violating a treaty.

Dr. Rapp said a computer can keep medical records but it can also be used to fire a missile. He said he could offer a good scientific rationale for studies involving cobra venom. Researchers should not be prevented from utilizing recombinant DNA technology simply on the outside chance some aspects could be converted to negative applications.

Dr. Davis said if DOD believes the Soviets are experimenting with cobra venom for biological warfare, it is not illegitimate for DOD to try to provide protection for the population. The NIH Guidelines address and permit the safe cloning of cobra venom toxin genes.

Dr. Gottesman said Mr. Rifkin requests that RAC develop scenarios for using recombinant DNA technology for biological warfare but is upset that the CIA is asking molecular biologists to develop such scenarios. She questioned whether any group could discuss scenarios without the possibility these scenarios would be used.

Mr. Rifkin said the difference between what he and the CIA was requesting was "like night and day." He said he was suggesting RAC:

> "...take a look at all of the potential implications for this technology so that you could draft appropriate guidelines and recommendations on how to best assure that we do not convert technology that was designed for one purpose to another unstated purpose."

Mr. Rifkin said he was not requesting RAC investigate violations of the Biological Weapons Convention. Rather he was requesting RAC study the potential military uses of this technology "so you can inform us on how we can safeguard ourselves so that this won't be used improperly."

Mr. Rifkin said RAC has evaluated the ethics of certain categories of recombinant DNA experiments. He said: "If the RAC committee has, and I know it has in the past, looked at the ethics of a particular type of experiment in relation to their risk, I don't understand why this kind of experiment should somehow be outside of its purview."

Mr. Rifkin said the NIH Guidelines deal with safety aspects of experiments. The DOD is in compliance with the safety aspects described in the NIH Guidelines but the ethics and merits of the experiments were not considered. The DOD may, thus, continue to perform all types of experiments as long as they are in compliance with the safety aspects of the NIH Guidelines. Mr. Rifkin said RAC will simply continue to say it has no responsibility. He said: "That seems to me to be not only unacceptable, but unconscionable from the point of view of the responsibilities of this committee."

Dr. Walters said RAC is not the appropriate committee for this type of evaluation. RAC is a reactive group. When a new application of recombinant DNA technology appears, RAC reacts by developing ground rules for that area of research. RAC has never performed studies of the type suggested by Mr. Rifkin.

Dr. Walters said Mr. Rifkin's proposal would create a working group of high visibility but very little substance. He suggested there were better ways for Mr. Rifkin to pursue his goals.

Dr. Johnson pointed out that RAC is not a regulatory authority or an investigative body. He thought RAC should continue to function as an advisory group.

Mr. Rifkin suggested RAC was "in a bind" because RAC has responsibility for approving DOD experiments but doesn't believe it has responsibility for overseeing or commenting on them. He suggested RAC indicate to DOD and Congress that RAC does not believe it should have the job of overseeing DOD experiments. He said:

> "...if this committee doesn't want to take a look at the implications of what it's clearing in terms of experiments, then it ought to just get out of the business of clearing experiments and give it back to the DOD or some other agency or the Congress to resolve."

Mr. Rifkin asked that a RAC member offer this suggestion as a motion.

Dr. Martin moved that RAC not establish a working group as requested by the Foundation on Economic Trends. The motion was seconded by Dr. Joklik.

Dr. Landy asked whether a motion was necessary. He asked Drs. Martin and Joklik whether they would consider the "no motion" option, i.e., offer no motion on the proposal.

Dr. Martin preferred to offer a motion because a motion indicates the request was seriously considered and a decision reached.

Dr. Davis moved to table Dr. Martin's motion. The motion to table was seconded.

By a vote of six in favor, thirteen opposed, and no abstentions, the RAC refused the motion to table Dr. Martin's motion.

Dr. Walters expressed concern that a motion that does not offer a rationale for RAC's conclusion may be misleading. He suggested a subgroup develop a rationale. Dr. Martin accepted this suggestion as an amendment to his motion.

Dr. Talbot asked whether the minutes of the May 3, 1985, RAC meeting could serve as the rationale. Mr. Mitchell expressed concern that the minutes will contain "a tremendous amount of material, some relevant and some perhaps irrelevant." The meeting was then recessed for lunch.

After lunch, Dr. Martin withdrew his motion; Dr. Joklik, the seconder of the motion, agreed.

There being no motion on the subject, Mr. Mitchell ruled the matter closed. He then asked Drs. Walters and Martin to assist him in considering whether a statement setting forth RAC's concerns about this issue should be developed.

Mr. Rifkin asked whether DOD would be required to submit classified experiments to the NIH for review. He asked if there are security clearance provisions for RAC members for review of classified materials.

Dr. Gartland replied that the vast majority of experiments conducted by DOD, as with any university or commercial concern, would be generically covered by the NIH Guidelines and would not be individually submitted to NIH for RAC review. He said the NIH Guidelines did not have any provisions for security clearance.

VI. REPORT OF RISK ASSESSMENT SUBCOMMITTEE

Dr. Gottesman said a series of questions (tab 1223) involving recombinant DNA risk assessment had originated in the Office of the Assistant Secretary for Planning and Evaluation (ASPE) of the Department of Health and Human Services (DHHS). This memorandum had been forwarded by the Assistant Secretary for Health, HHS, to several HHS agencies (Food and Drug Administration, Centers for Disease Control, and National Institutes of Health) for comment. The Director, NIH, suggested the Risk Assessment Subcommittee address these questions, and the Assistant Secretary for Health concurred with this proposal.

Dr. Gottesman, Chair of the Risk Assessment Subcommittee, said she had polled subcommittee members on the issues and had collated the responses in order to develop a preliminary draft response to the ASPE memorandum. The subcommittee met by telephone conference call (tab 1223) on October 15, 1984, to evaluate this preliminary draft response. Specific responses to the ASPE questions were also previously discussed at the October 29, 1984, RAC meeting (tab 1222).

Dr. Clowes said the Risk Assessment Subcommittee had addressed the question of whether the NIH Guidelines continue to be valid in light of new information generated in the past few years. The subcommittee agreed this information had been taken into consideration when the NIH Guidelines were designed or revised, and that certain sections of the NIH Guidelines were based on "worst case scenarios." The new information, thus, did not affect the validity of the NIH Guidelines.

Dr. Gottesman said the field of retrovirology is developing very rapidly and the subcommittee felt additional expertise should be sought to adequately address issues involving retroviruses. She proposed a discussion group with appropriate expertise be formed. The discussion group could attempt to "thrash out some of the issues" on retroviruses.

Drs. Friedman and Wensink agreed a discussion group on retroviruses would be helpful. Mr. Mitchell said any RAC members interested in participating in such a discussion group should contact ORDA.

VII. REPORT OF WORKING GROUP ON HUMAN GENE THERAPY

Dr. Walters, Chair of the RAC Working Group on Human Gene Therapy, said the working group had developed a guidance document (tabs 1201, 1213, 1214, 1215) entitled "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols" (Attachment III).

Dr. Walters said this guidance document begins with an introduction to human somatic-cell gene therapy. Part I, entitled "Description of Proposal", requests first the objectives and rationale of the gene therapy protocol. The document subsequently poses a series of issues which parallel the general DHHS regulations for all research involving human subjects including research design, anticipated risks and benefits, selection of subjects, informed consent, and privacy and confidentiality. Part II of the document raises issues that are not usually evaluated by local review committees. One such issue is appropriate provision for sharing information with the public in a timely and accurate fashion. Part III of the points to consider outlines requested documentation and Part IV, reporting requirements.

Dr. Walters said the points to consider document had been published for public comment in the January 22, 1985, Federal Register; fifteen letters were received in response to this announcement.

Some modifications (tab 1213) have been introduced into the document in response to these comments. For example, the document's introduction more clearly accents the difference between somatic-cell and germ line gene therapy. The introduction reviews the multi-year process of public discussions concerning gene therapy. It now includes a quote from the December 1984 Office of Technology Assessment paper, Human Gene Therapy, which states:

> "Civic, religious, scientific, and medical groups have all accepted, in principle, the appropriateness of gene therapy of somatic cells in humans for specific genetic diseases. Somatic cell gene therapy is seen as an extension of present methods of therapy that might be preferable to other technologies."

Dr. Walters said the revised document now asks about information on prior laboratory studies in non-human primates and/or other laboratory animals. The phrase "and/or other laboratory animals" has been added to this version of the points, and indicates the working group's willingness to consider human gene therapy proposals on a case-by-case basis before the completion of laboratory studies in multiple species of animals.

Dr. Walters said the document has also been modified to request an agreement by prospective patients or their guardians to permit long-term follow-up and

an autopsy in the event of the patient's death. Both of these stipulations, in the opinion of the working group, are reasonable constraints on the autonomy of patients and their families in light of the benefits to future gene therapy patients.

Dr. Walters said some commentors had suggested the working group should possess additional types of expertise. The working group accepts this criticism but notes that no group of 15 people can "cover all the bases." The working group is committed, however, to obtaining additional expertise by consulting with ad hoc consultants as necessary.

Dr. Walters said the working group was presenting these points to consider not as a finished code of rules but rather as a checklist of the most important issues raised by the many thoughtful people who have discussed human gene therapy.

Dr. Walters said the working group will devote further study to two topics: (1) measures to disarm retroviral vectors; and (2) technical problems currently associated with germ line gene modifications in animal systems. In the future, the working group will devote detailed attention to specific ethical and legal questions surrounding gene therapy.

Dr. Walters then thanked the members of the working group, the liaison members, and ORDA staff for their efforts. He also thanked the individuals who commented on the points to consider document.

Dr. Walters identified a problem with the current version of the document: footnote one indicates the points to consider apply to both recombinant RNA and recombinant DNA. The current NIH Guidelines, however, do not officially cover recombinant RNA. He said Dr. Gottesman has a proposal for resolving this problem.

Dr. Gottesman proposed to modify footnote one of the points to consider document by eliminating the first sentence and the words "as well as to RNA" in the second sentence. The footnote would then read: "Section III-A-4 applies to both recombinant DNA and DNA derived from recombinant DNA." In addition, a proposal to modify the NIH Guidelines to cover RNA derived from recombinant DNA could be developed and published prior to the next RAC meeting.

Dr. Friedman said the working group did an excellent job in preparing the points to consider document.

Dr. Rapp said "the continuous request of certain individuals" to have a representative "of every stripe" on the Working Group for Human Gene Therapy is nonsensical. He said the major issues are how safe is the procedure and how can the interests of society be protected. The working group as currently constituted has been working well in dealing with scientific and social issues.

Dr. Davis specifically disagreed with the suggestion that a representative of industry be added to the working group; such an addition might give the mistaken impression that human gene therapy is or will soon be a large-scale industrial activity.

Mr. Robert Lanman, the NIH legal advisor, argued that the points to consider should not request a copy of the patient consent form. Dr. Walters said questions about the quality of consent forms have recently been raised for some innovative therapies. Mr. Mitchell said the working group was very sensitive about this issue and felt in the initial trials the consent form should be above reproach.

Dr. Rapp said human gene therapy protocols will be asking for agreements different from those requested in most clinical investigations. For example in human gene therapy protocols, the subject will be asked to participate in long-term followup and to give autopsy permission in advance. For this reason, he thought the working group should look at the consent forms for the initial gene therapy protocols.

Dr. Miller said FDA has several comments on the points to consider document. He said the introduction of the document does not accurately represent FDA's role in regulating these products. The introduction implies FDA jurisdiction will begin only when somatic-cell gene therapy protocols become more widely applied and use manufactured biological materials. Dr. Miller said FDA does not regulate gene therapy or technologies per se, but does regulate new drug products as defined in regulations. Dr. Miller said FDA has regulatory jurisdiction when a new drug product is used to effect human gene therapy, and FDA will indeed be overseeing human gene therapy experiments.

Dr. Miller proposed the following language be substituted for the last sentence of item (5) of the document's Introduction: "For information on the jurisdiction of the Food and Drug Admininstration over products employed for human gene therapy, please refer to the FDA's Statement of Policy."

Dr. Miller said item (8) of the Introduction misrepresents the aim of germ line therapy by stating the aim is "changing the set of genes passed on to the individual's offspring." He continued:

> "...in general, the object of gene therapy is to the cure the individual who will result from the embryo that is being manipulated. The effects on subsequent generations are usually a secondary effect and indeed the object is to cure that individual."

Referring to item (11) of the Introduction, Dr. Miller said "we believe [this item] states the question that any degree of teratogenesis is not acceptable." He said in conventional medical interventions. clearly that is not the case. Oblative radiotherapy before a bone marrow transplant, for example, for leukemia is considered acceptable. Oblative radiotherapy produces sterilization, and the risks to benefits in that situation are considered appropriat. Similarly, certain regimens of chemotherapy induce sterility or are clearly

teratogenic. Teratogenesis per se should not rule out a proposed medical intervention.

Dr. Miller said the document's request in Section I-B-3-e for information on the major anticipated potential beneficial and adverse effects of the treatment and on measures taken to control or reverse adverse effects "are really causes for speculation that's so complex as to be unreasonable."

Dr. Miller said the question in Section I-B-4-a of the document asking on what basis the potential public health benefits or hazards are postulated "is so ambiguous that it would be very difficult to answer and adds very little to the document."

Dr. Miller suggested a point H be added to Part III of the document. That point would ask:

> "What administrative official in the hospital, clinic or other institution has approved of this procedure?"

Dr. Miller said:

> "...we strongly believe...that since somatic cell gene therapy is an extension of present methods of therapy and is wholly analogous to conventional medical intervention, that decisions on individual protocols should be made in a way that is consistent with other conventional therapies; that is, primarily by physicians and scientists with expertise in the area. An NIH study section or an FDA advisory committee in a given discipline would not be composed largely of public policy specialists and bioethicists and attorneys. It would be comprised of clinicians and scientists with expertise in the area; and we feel strongly that the working group that evaluates such proposals should be comprised of persons largely with expertise in that area and not in these other areas as is presently the case."

Dr. Walters said the working group would like to obtain RAC's opinion on the April 15, 1985, version of the points to consider document. The working group will over the course of the next year be fine-tuning the document, and any major changes the working group might propose would be submitted to RAC for its consideration.

Dr. Walters felt the document should be circulated as soon as possible as representing RAC's best judgment on appropriate ground rules for this area of research and potential therapy.

Dr. Landy moved that RAC accept the points to consider document with appreciation. Minor changes can be made in the document without resubmitting the points to consider for RAC review. Significant changes would, however, be discussed by the RAC. This motion was seconded by Dr. Joklik.

Dr. Davis said he did not know if it is necessary to vote on this points to consider document.

Dr. Miller said FDA would be very disturbed if the document were issued, even in preliminary form, without first making some of the changes he requested since the current document "is grossly inaccurate." He said a perception already exists this version is the final version of the points to consider document; the magazine "Science" has indeed assumed incorrectly this version is the final document. Dr. Miller said:

> "I think that is an inaccurate representation and that's the kind of misinformation that is promulgated when corrections are not made and things are published prematurely."

Mr. Mitchell said the points to consider document was first published to obtain public comment in the January 22, 1985, Federal Register. No indication was given that this document was final.

Dr. Gottesman said she thought two changes could be made immediately: the changes in footnote one and Dr. Miller's first suggestion (for item (5) of the Introduction) concerning FDA's jurisdiction. She said the other changes suggested by Dr. Miller would require further discussion.

Dr. Walters said some of the modifications proposed by Dr. Miller had been discussed by the working group and a deliberate decision made not to accept them. Dr. Walters said he would not wish to incorporate Dr. Miller's proposed changes without the working group's knowledge or consent. He suggested the more substantive of Dr. Miller's modifications be sent to the working group for reconsideration.

Dr. Davis suggested the language concerning the purpose of germ line gene therapy be modified.

Dr. Gottesman said language discussing the purpose of germ line gene therapy can be ambiguous depending on whether one is thinking of the adult or the embryo. She agreed this language might be clarified but felt further discussion was necessary; she could not agree to a quick modification.

Mr. Mitchell agreed more discussion was required; he said RAC should avoid language which might cause confusion.

Dr. Davis suggested the points to consider document be returned to the working group for reconsideration.

Dr. Gottesman reiterated her suggestion that RAC approve the points to consider document as a working document with the two changes she had mentioned (i.e., in footnote one and in item (5) of the Introduction). Dr. Miller's other suggested modifications would be discussed at a future meeting of the working group. Dr. Gottesman said the points to consider document could be sent in the interim to investigators seeking guidance for proposal submission.

Dr. Landy said he could not agree with Dr. Davis' suggestion to return the points to consider document to the working group without RAC endorsement. He preferred a "working" document to a "perfect" document.

Mr. Mitchell said RAC could approve this points to consider document as a working document at this time with the understanding that modification is an ongoing process.

Dr. Miller said:

> "The only remaining problem we would have with that is that we feel that some of the nuances of wording and meaning that I described were not appreciated fully by the working group and by going back to them I think wouldn't be of much avail.
>
> "I think part of the problem of the working group takes me back to the last of FDA's points, that it's a group constituted largely of public policy people, lawyers and bioethicists with really a minority of clinicians and molecular biologists who don't understand completely some of these issues."

Dr. Landy asked whether Dr. Miller was requesting that RAC act as a board of appeal on the language of the document.

Dr. Miller said he was and said that: "we would prefer, of course, that this document is not promulgated in the interim with some of these errors still in them."

Dr. Saginor suggested the language on teratogenicity might be reconsidered since many drugs currently in use have teratogenic or other side effects. He suggested the document be approved as a working document, and the modifications suggested by Dr. Miller be evaluated carefully before the next RAC meeting.

Mr. Mitchell suggested the document could be approved as a working document which could be reviewed by the RAC at its next meeting. Dr. Saginor said this would be a reasonable approach.

Dr. Miller said he could not agree with this approach because of the "misconceptions" that result. He said: "I think again we haven't broached the issue of the composition of the group that will actually decide on these proposals which, as we all agree, are largely scientific and medical issues of prime importance."

Dr. Davis asked why RAC could not simply wait until the next RAC meeting to take action. He did not think investigators would be delayed if the document was not approved by RAC as a working document.

Dr. Gottesman disagreed with Dr. Davis' approach. She said the alleged "misconceptions" are not quite as dramatic as Dr. Miller paints them. Several of these comments were not made previously by Dr. Miller to the

working group in the form made at the May 3, 1985, RAC meeting, thus, it is not accurate to suggest the working group rejected these suggestions without careful consideration.

Dr. Gottesman thought not adopting the document would create problems. She said the question before RAC is whether this document is so drastically flawed it should not be adopted.

Dr. Walters said the differences of opinion existing between Dr. Miller and the working group cannot simply be attributed to differences between the scientific and nonscientific communities. Dr. Walters said distinguished scientists such as Drs. Howard Temin, W. French Anderson, and Arno Motulsky are members of the working group. These individuals have given a great deal of time and effort to developing the precise scientific language in the document. The document represents the best judgment of the working group on what is required to protect the first recipients of human gene therapy.

Mr. Mitchell said Dr. Miller had questioned the qualifications of the working group. He said RAC should satisfy itself that the working group possesses the requisite expertise. Mr. Mitchell said an effort had been made in constituting the working group to obtain expertise in a broad spectrum of disciplines. The intent was to obtain expert clinicians, scientists, ethicists, lawyers, and public policy people. The working group was constituted in this manner to address concerns raised by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.

Dr. Friedman said he did not see why Dr. Miller was so concerned with what "Science" publishes. He supported the suggestion that the points to consider document be used as a working document open to further revision.

Dr. Landy said he wished to modify his motion to emphasize that the points to consider would be a working document, and to acknowledge the FDA comments which will be considered at the next RAC meeting or by the working group.

Dr. Martin said the two modifications suggested by Dr. Gottesman could be introduced in the points to consider document and the document republished for comment. The RAC at the next meeting could respond to any comments received including Dr. Miller's comments.

Dr. Rapp supported this suggestion. He did not think RAC should override the working group but should ask them to reconsider these issues. Dr. Rapp suggested RAC accept the current points to consider as a working document. He said there is some urgency in developing a document which can be sent to investigators; he thought it would be a mistake to hold up the document for several more months when the current points to consider form a perfectly reasonable document. He called the question.

Dr. Landy restated his motion that the RAC accept with thanks the points to consider with the two modifications suggested by Dr. Gottesman (i.e., in

footnote one and in item (5) in the Introduction) as a current working document, republish it for comment, and consider it again at the next RAC meeting.

By a vote of twenty in favor, none opposed, and one abstention, the RAC accepted the motion. Mr. Daloz abstained.

VIII. PROPOSAL FOR A COORDINATED FRAMEWORK FOR REGULATION OF BIOTECHNOLOGY

Mr. Mitchell said this agenda item (tabs 1208, 1211) addresses a proposal for a coordinated framework for regulation of biotechnology. The December 31, 1984, Federal Register proposed a review mechanism for the oversight of biotechnology. The notice stated its purpose was to provide a concise index of U.S. laws related to biotechnology, to clarify the policies of the major regulatory agencies involved in reviewing research and products of biotechnology, to describe a scientific advisory mechanism for assessment of biotechnology issues, and to explain how the activities of the Federal agencies in biotechnology will be coordinated.

Mr. Mitchell said a special working group, the RAC Working Group on Biotechnology Coordination, had been formed to comment on the December 31, 1984, Federal Register notice. Mr. Mitchell, Chair of the Working Group on Biotechnology Coordination, constituted the group because the deadline for comment on the Federal Register proposal was April 1, 1985, while the next RAC meeting was May 3, 1985. He said the working group met for one day and attempted to offer some suggestions and observations.

Mr. Mitchell said several major points were made by the working group. For nearly ten years the NIH Guidelines have been the sole standard for the oversight of recombinant DNA experiments. Not only have scientists and industrial concerns in this country followed these NIH Guidelines, but other countries have adopted them as national standards. In addition, localities in the U.S. have based ordinances on the NIH Guidelines. The working group questioned how the proposal would affect countries and municipalities which have adopted the NIH Guidelines.

Mr. Mitchell said another concern was how the December 31, 1984, proposal would affect the flexibility of the NIH Guidelines. Until this time, RAC and NIH have had authority to modify the NIH Guidelines as knowledge accumulated. The working group feared such flexibility might be lost under the December 31, 1984, proposal.

Mr. Mitchell said the working group also expressed concern about public participation. The group asked whether the proposed advisory committees which would be established in other agencies would have public members and to what extent these members would participate meaningfully. In addition, in order for public confidence to be maintained, agency discussions should be open to public scrutiny. If the subject matter is fragmented between five different agencies, where would the public go to participate in discussions?

Mr. Mitchell said the working group felt the cooperation and confidence of scientific investigators must be maintained. A very bureaucratic and complex system would have a chilling effect on the scientific community. It is also necessary to maintain the confidence of industry and of the public.

Mr. Mitchell said the RAC working group suggested a distinction should be drawn between regulating products and regulating processes.

Mr. Mitchell said the working group also considered the structure of the proposed oversight mechanism. The issue appeared to working group members to boil down to whether a single agency approach or a federation of agencies is more efficient. A loose federation of agencies can work; the question is how the agencies will be coordinated and which agency will assure coordination. The more the working group considered the matter, the more it appeared a single review committee with appropriate working groups might be a better oversight mechanism. Mr. Mitchell said he had sent a letter expressing these working group concerns to the Cabinet Council Working Group on Biotechnology.

Dr. Gottesman said the most important points in the Working Group on Biotechnology Coordination discussion were: (1) Research should not be subjected to any additional regulation. The working group appeared to define research and application differently than the December 31, 1984, proposal. (2) How will the various agencies fulfill their oversight function? For example, will the agencies be required to review every document submitted? Will most reviews be performed by in-house agency staff? Would advisory groups only deal with policy? How the advisory groups are set up will differ depending on what is expected of them.

Dr. Clowes said the RAC working group viewed the proposed oversight mechanism as too complicated. The proposed mechanism adds an extra level of regulation and may lead to a lack of coordination and uniformity of review. The major problem, however, is that the proposed mechanism may not provide the continuity of experience RAC has provided. The Federal Register proposal would replace an effective organization with new and untried bodies which may need time to learn to function effectively. In the interim, a climate of insecurity may result; and this climate would likely have a negative effect on scientific progress and on its commercial application.

Dr. Clowes said he would like to offer the concept of an expanded RAC as a potential alternative solution to the complicated structure proposed in the December 31, 1984, Federal Register. Modifications could be made in the present structure and could take the form of additional working groups with greater cooperation and interaction from other agencies. These working groups might function as voting members of the RAC. This modified structure would retain the experience, confidence, and goodwill RAC has built up over the years. Dr. Clowes said he and several other members of the working group would prefer such a structure.

Dr. Friedman said the working group's primary concern is that research not be overregulated. Many members of the working group had a sense of deja vu in reading the Federal Register proposal and thought the wheel was being reinvented. Ten years of experience have permitted RAC to answer many of the questions raised in the December 31, 1984, Federal Register. Dr. Friedman said many members of the working group were concerned that RAC's collective experience be maintained and used.

Dr. Johnson said a clear contrast exists between the RAC system and the complexity of the proposed system. He felt the proposed system is redundant and will be inhibitory to the fragile U.S. lead in biotechology.

Dr. Johnson also thought the Federal Register proposal was written from the perception that products of biotechnology are "different" and that a different set of rules have to be designed to regulate and evaluate them. He did not think biotechnology products differed from products produced by other processes.

Dr. Johnson said the December 31, 1984, document contains policy statements by the FDA, the USDA, and the EPA. The FDA and the USDA essentially state that they possess sufficient authority to regulate products on a case-by-case basis in their area of jurisdiction. The EPA on the other hand appears to be attempting to regulate research. Moreover, they claim jurisdiction over products designed by processes that have been completely unregulated for many years, e.g., cell fusion, undirected, and site-directed mutagenesis. The EPA, thus, raises the spectre of handling research proposals differently if the ultimate intent is to commercialize. This is "regulation by intent." Dr. Johnson said the words "laboratory" and "experimental" should be defined and used consistently.

Dr. Pirone agreed and suggested the concept of laboratory be broadened to include all experimental protocols conducted in growth chambers, greenhouses, and perhaps even small-scale plots. Dr. Pirone said he was particularly concerned about how basic research in plant and animal sciences would fare under the December 31, 1984, Federal Register proposal. The proposal is vague about the review process; and research in plant and animal sciences might be overseen by USDA, EPA, NIH, or the National Science Foundation (NSF) depending on the considered intent of the experiments.

Dr. Walters said he had two primary concerns about the document published in the December 31, 1984, Federal Register. The first concern is a lack of emphasis on public discussion and debate at either the level of the scientific advisory committees or the oversight board. The Federal Register document does not contain a clear commitment to a public process. The second concern is that the document views too narrowly the mission of the advisory committees and the oversight board. In many cases, the advisory committees and the oversight board will be dealing with value judgments and not simply the gathering of scientific facts. Dr. Walters said these committees should possess not only the best scientific expertise available but also expertise in disciplines such as political science, law, and ethics.

Dr. Martin said the December 31, 1984, Federal Register proposal is an "enormous can of worms." He thought it posed significant threats to recombinant DNA technology, medical research, and the U.S. economy. He argued that if U.S. industries are not successful in first applying this technology and capturing markets, the U.S. will experience a loss of jobs, particularly for skilled and academically trained individuals.

Dr. Joklik agreed with Dr. Martin, and supported Dr. Clowes' suggestion; he thought expanded use of working groups and subcommittees under RAC's purview would be much preferable to the plan proposed in the December 31, 1984, Federal Register.

Dr. Pramer said a consistent feature of those comments he had seen is a recognition of RAC and its activities. The American Society for Microbiology (ASM) comment on the Federal Register proposal spoke in favor of continuing with a single review body rather than with a number of separate units. ASM expressed concern that differences in policy and procedures might exist with separate oversight bodies, and it wouldn't take long for individuals or institutions to find the path of least resistance.

Mr. Mitchell asked Dr. Talbot how RAC might appropriately continue to have a meaningful role in the development of oversight of biotechnology. RAC has a unique background of experience and should continue to play a role in this process.

Dr. Talbot said the comments made at the RAC meeting will be transmitted to the NIH Director. The Director represents the NIH at the Cabinet Council Working Group.

Dr. Talbot said if the other responses received by the Cabinet Council Working Group contain similar comments, strong pressure will exist to revise the proposed structure towards a single RAC or a modified RAC. Negotiations between the various agencies must be held.

Dr. Gottesman said it might be useful to have some formal discussion of the issues with representatives of the Cabinet Council. She said RAC would be eager to participate in an exchange of concerns.

Dr. Edwin Shykind who identified himself as a member of the Cabinet Council Working Group said he would report RAC's request. He said the RAC and the Cabinet Council Working Group should attempt to work together closely.

Dr. Carl Mazza of the EPA said the comments received in response to the December 31, 1984, Federal Register are being read very carefully by the various regulatory agencies.

Dr. Mazza said U.S. regulatory laws are complex, and it's no surprise that a complex document developed from the attempt to describe all of these regulations in one document.

Dr. Mazza said the EPA is not attempting to regulate research in so far as appropriate given the mandate of the law. In the December 31, 1984, Federal Register, EPA attempted to describe the implications and the limitations of the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide and Rodenticide Act.

Dr. Mazza said EPA has responsibility for regulating certain commercial products. The EPA mandate for reviewing these products should mesh with the historical role of the RAC. Some problems may develop with this transition. The EPA is very interested in making the fit between the EPA and the RAC work.

Dr. Mazza supported the suggestion that more opportunities for exchange of information be created.

Ms. Anne Hollander of the EPA, said EPA in the December 31, 1984, Federal Register discusses in great detail a number of different technologies and requests scientific comment on the risk implications of these technologies. She asked RAC to address the question of whether the different technologies have different implications for risk. Ms. Hollander contended RAC itself is based on the premise there is something different about recombinant DNA technology.

Dr. Davis said U.S. regulatory laws may be complex but RAC and the scientific community are not concerned with the law's complexity. Rather they are concerned with the complexity of the December 31, 1984, Federal Register proposal. He hoped it was crystal clear that a great many people do not think the proposed oversight mechanism is a good one.

Dr. Davis said there was a difference in tone between the section of the December 31, 1984, Federal Register written by the EPA and those sections written by USDA and FDA. He said FDA and USDA expressed considerable confidence in the way RAC has been handling the issues and were willing to rely on RAC for general advice for fulfulling their responsibilities. The EPA document on the other hand is much longer, and raises all types of questions. He said he had written a lengthy criticism on the EPA section of the Federal Register announcement. He did not address in that letter any of the EPA's hypothetical scenarios because the document's basic assumption is that these organisms are a terribly dangerous set of organisms. He said he felt as if he "was in about 1974." Dr. Davis said in 1985 there is not much reason from a scientist's point of view to assume these organisms are all terribly dangerous.

Dr. Davis said the assumption DNA is a toxic chemical to be regulated under TSCA puts the whole discussion in a framework that makes it extremely difficult for scientists to even want to start answering such questions.

Mr. Mitchell said the Working Group on Biotechnology Coordination did not have time to comment specifically on EPA's questions. Rather the working group focused primarily on the effect of the December 31, 1984, Federal

Register on the NIH, the NIH Guidelines, and the RAC. Mr. Mitchell suggested perhaps the working group might now review EPA's suggestions in greater detail and offer some response.

Dr. Davis did not think it appropriate at this time for the RAC working group to comment further on the December 31, 1984, Federal Register. He suggested RAC await the Cabinet Council Working Group response to the comments received.

IX. PROPOSED AMENDMENT OF PART III OF THE GUIDELINES

Dr. Friedman said this proposal (tab 1205) had been submitted by Dr. Talbot. Dr. Friedman said Dr. Talbot noted that under the NIH Guidelines certain proposals are received by NIH for review by RAC and subsequent NIH approval. Recently other Federal agencies have taken steps toward assuming new roles in review of recombinant DNA proposals. Because of these developments, proposals submitted to the NIH for RAC review may also be submitted to another agency for review.

Dr. Friedman said Dr. Talbot suggested it would be advantageous for NIH to have the option of deferring to other Federal agencies. In order to give NIH this latitude, Dr. Talbot suggested a new sentence would be added at the end of Section III-A of the NIH Guidelines just before Section III-A-1 as follows:

> "If experiments in this category are submitted for review to another Federal Agency, the submitter should notify ORDA; ORDA may then determine that such review serves the same purpose, and based on that determination, notify the submitter that no RAC review will take place, no NIH approval is necessary, and the experiment may proceed upon approval from the other Federal agency."

Dr. Friedman said this proposal is an attempt to reduce paperwork. He supported Dr. Talbot's proposal.

Dr. Johnson felt the proposal did not clearly distinguish between oversight of products and oversight of experiments. He said he had no problem with Dr. Talbot's proposal if the proposal relates to regulation of products. He thought, however, that a single review body for evaluation of scientific issues should be in place.

Dr. Saginor asked whether Dr. Talbot's proposal referred to the review system proposed in the December 31, 1984, Federal Register or to the current system. Dr. Talbot said his proposal refers to the current system. For example, under the current system the Lindow/Panopoulos proposal involving the ice-minus bacteria was reviewed by both the NIH and the EPA.

Dr. Mills questioned whether other agencies would perform a type of review equivalent to RAC review. If review systems equivalent to RAC's exist, Dr. Mills said he would support Dr. Talbot's proposal.

Dr. Talbot pointed out that this proposal would give the NIH the option to defer to another agency. The proposal does not require the NIH to defer. The NIH currently does not have this option.

Mr. Clarence Styron of Monsanto Company asked whether Dr. Talbot's proposal had any implication for IBCs. Dr. Talbot replied it would have no implications for IBCs.

Dr. Miller said FDA feels: "there is now clear redundancy of oversight, between FDA and NIH, and USDA and NIH, and EPA and NIH, and FDA is disturbed by that."

Dr. Miller said while FDA supports the concept of relieving this redundancy, FDA did not think Dr. Talbot's proposal was the "optimal approach." FDA has three reservations: (1) there would be some uncertainty among individual investigators or industry about whether an exemption would be granted by ORDA; (2) some bureaucracy would be created at NIH and by the investigators or companies "to deal with correspondence, phone calls, meetings, requests to NIH;" (3) there is some ambiguity about the broadness of the exemption, i.e., if an investigator slightly changed his protocol, would he have to come back to NIH again.

Dr. Miller said:

> "...what we would prefer to see is some kind of categorical exemption so that an investigator who was being regulated by another federal agency would be exempt from oversight by NIH or perhaps it could be done more specifically so that oversight under specific federal statutes such as the Food, Drug, and Cosmetic Act, the Public Health Service Act, the USDA's Virus, Serum, and Toxin Act and perhaps others, EPA's statutes for example, would automatically be exempt from NIH oversight."

Dr. Miller said this type of exemption is done with TSCA; EPA is exempted from jurisdiction over products overseen by FDA's statutes.

Dr. Miller said he will formally propose this type of exemption in the Federal Register announcing the next RAC meeting and was now proposing that official action on Dr. Talbot's proposal be deferred until the next RAC meeting.

Dr. Sue Tolin of the USDA said USDA would like to see Dr. Miller's proposal of a categorical exemption be presented to RAC; and, therefore, feels approval of Dr. Talbot's proposal at the May 3, 1985, meeting would be premature particularly in light of the discussions occurring at this time in the Cabinet Council Working Group. She supported the request to defer action on this proposal.

Dr. Johnson moved that RAC table Dr. Talbot's proposal. Dr. Walters seconded the motion.

By a vote of seventeen in favor, none opposed, and no abstentions, the RAC accepted the motion to table the proposal.

X. ORDA PROPOSAL REGARDING RECEIPT OF APPLICATION SUMMARIES

Dr. Gartland said this proposal (tab 1212) developed from the December 31, 1984, Federal Register proposal for a coordinated framework for regulation of biotechnology. The Federal Register states:

> "Each agency will promptly send to its advisory committee a summary of each application relating to recombinant RNA, recombinant DNA, or cell fusion submitted to it for funding or administrative review, regardless of whether the agency is requesting a scientific review. The advisory committee may decline to receive summaries...."

Dr. Gartland said the number of summaries RAC would receive under this Federal Register language would be massive; thousands of such grant applications are submitted to NIH each year. He said RAC has never requested to see all of the grant applications submitted to the NIH. He proposed that the RAC decline to receive such grant application summaries since provision of such summaries to RAC would involve a tremendous workload with little or no benefit.

Dr. Walters moved that RAC accept the proposal. The motion was seconded by Dr. Gottesman.

By a vote of fifteen in favor, none opposed, and no abstentions, RAC accepted the motion.

XI. FUTURE MEETING DATES

Dr. Gartland said the next meeting of the RAC is scheduled for September 23, 1985. Mr. Mitchell said some working group meetings might also be held in the interim between the May 3 and September 23, 1985, RAC meetings.

XII. ANNOUNCEMENT ON A SYMPOSIUM ON ENGINEERED ORGANISMS IN THE ENVIRONMENT

Dr. Sharples said ASM is organizing a cross-disciplinary symposium entitled "Engineered Organisms in the Environment: Scientific Issues." This meeting will be held in Philadelphia, Pennsylvania, on June 10-13, 1985.

Dr. Sharples said the meeting is to identify the scientific issues and sort out the less important issues from the critical issues in this area. She urged interested individuals, including RAC members, to attend this meeting.

XIII. ADJOURMENT

Dr. Gottesman moved that the RAC adjourn. The motion was seconded. Mr. Mitchell ruled the May 3, 1985, RAC meeting adjourned at 4:15 p.m.

Respectfully submitted,

Elizabeth Milewski

Elizabeth A. Milewski, Ph.D.
Rapporteur

William J. Gartland, Jr., Ph.D.
Executive Secretary

I hereby certify that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

9/23/85
Date

Robert E. Mitchell, LL.B.
Chair
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May 3, 1985

DRAFT 1202 DRAFT

POINTS TO CONSIDER FOR SUBMISSIONS INVOLVING TESTING IN THE ENVIRONMENT OF MICROORGANISMS DERIVED BY RECOMBINANT DNA TECHNIQUES

Experiments in this category require specific review by the Recombinant DNA Advisory Committee (RAC) and approvals by the National Institutes of Health (NIH) and the Institutional Biosafety Committee (IBC) before initiation. The IBC is expected to make an independent evaluation although this evaluation need not occur before consideration of an experiment by the RAC. Relevant information on the proposed experiments should be submitted to the Office of Recombinant DNA Activities (ORDA). The objective of this review procedure is to evaluate the potential environmental effects of testing of microorganisms that have been modified by recombinant DNA techniques.

These following points to consider have been developed by the RAC Working Group on Release into the Environment as a suggested list for scientists preparing proposals on environmental testing of microorganisms, including viruses, that have been modified using recombinant DNA techniques. The review of proposals for environmental testing of modified organisms is being done on a case-by-case basis because the range of possible organisms, applications, and environments indicate that no standard set of procedures is likely to be appropriate in all circumstances. However, some common considerations allow the construction of points to consider such as those below. Information on all these points will not be necessary in all cases but will depend on the properties of the parental organism and the effect of the modification on these properties.

Approval of small-scale field tests will depend upon the results of laboratory and greenhouse testing of the properties of the modified organism. We anticipate that monitoring of small-scale field tests will provide data on environmental effects of the modified organism. Such data may be a necessary part of the consideration of requests for approval of large-scale tests and commercial applications.

I. Summary

Present a summary of the proposed trial including objectives, significance, and justification for the request.

II. Genetic Considerations of Modified Organism to be Tested

A. Characteristics of the Nonmodified Parental Organism

1. Information on identification, taxonomy, source, and strain.

2. Information on organism's reproductive cycle and capacity for genetic transfer.

B. Molecular Biology of the Modified Organism

1. Introduced Genes

a. Source and function of the DNA sequence used to modify the organism to be tested in the environment.

b. Identification, taxonomy, source, and strain of organism donating the DNA.

2. Construction of the Modified Organism

a. Describe the method(s) by which the vector with insert(s) has been constructed. Include diagrams as appropriate.

b. Describe the method of introduction of the vector carrying the insert into the organism to be modified and the procedure for selection of the modified organism.

c. Specify the amount and nature of any vector and/or donor DNA remaining in the modified organism.

d. Give the laboratory containment conditions specified by the NIH Guidelines for the modified organism.

3. Genetic Stability and Expression

Present results and interpretation of preliminary tests designed to measure genetic stability and expression of the introduced DNA in the modified organism.

III. Environmental Considerations

The intent of gathering ecological information is to assess the effects of survival, reproduction, and/or dispersal of the modified organism. For this purpose, information should be provided where possible and appropriate on: (i) relevant ecological characteristics of the nonmodified organism; (ii) the corresponding characteristics of the modified organism; and (iii) the physiological and ecological role of donated genetic sequences in the donor and in the modifiel organism(s). For the following points, provide information where possible and appropriate on the nonmodified

organism and a prediction of any change that may be elicited by the modification.

A. Habitat and Geographic Distribution

B. Physical and Chemical Factors which can Affect Survival, Reproduction, and Dispersal

C. Biological Interactions

1. Host range.

2. Interactions with and effects on other organisms in the environment including effects on competitors, prey, hosts, symbionts, predators parasites, and pathogens.

3. Pathogenicity, infectivity, toxicity, virulence, or as a carrier (vector) of pathogens.

4. Involvement in biogeochemical or in biological cycling processes (e.g., mineral cycling, cellulose and lignin degradation, nitrogen fixation, pesticide degradation).

5. Frequency with which populations undergo shifts in important ecological characteristics such as those listed in III-C points 1 through 4 above.

6. Likelihood of exchange of genetic information between the modified organism and other organisms in nature.

IV. Proposed Field Trials

A. Pre-Field Trial Considerations

Provide data related to any anticipated effects of the modified microorganism on target and nontarget organisms from microcosm, greenhouse, and/or growth chamber experiments that simulate trial conditions. The methods of detection and sensitivity of sampling techniques and periodicity of sampling should be indicated. These studies should include, where relevant, assessment of the following items:

1. Survival of the modified organism.

2. Replication of the modified organism.

3. Dissemination of the modified organism by wind, water, soil, mobile organisms, and other means.

B. Conditions of the Trial

Describe the trial involving release of the modified organism into the environment:

1. Numbers of organisms and methods of application.

2. Provide information including diagrams of the experimental location and the immediate surroundings. Describe characteristics of the site that would influence containment or dispersal.

3. If the modified organism has a target organism, provide the following:

   a. Identification and taxonomy.

   b. The anticipated mechanism and result of the interaction between the released microorganism and the target organism.

C. Containment

Indicate containment procedures in the event of accidental release as well as intentional release and procedures for emergency termination of the experiment. Specify access and security measures for the area(s) in which the tests will be performed.

D. Monitoring

Describe monitoring procedures and their limits of detection for survival, dissemination, and nontarget interactions of the modified microorganism. Include periodicity of sampling and rationale for monitoring procedures. Collect data to compare the modified organisms with the nonmodified microorganism most similar to the modified organism at the site of the trial. Results of monitoring should be submitted to the RAC according to a schedule specified at the time of approval.

V. Risk Analysis

Results of testing in artificial contained environments together with careful consideration of the genetics, biology, and ecology of the nonmodified and the modified organisms will enable a reasonable prediction of whether or not significant risk of environmental damage will result from the release of the modified organism in the small-scale field test. In this section,

the information requested in Sections II, III, and IV should be summarized to present an analysis of possible risks to the environment in the test as it is proposed. The issues addressed might include but not be limited to the following items:

A. The Nature of the Organism

1. The role of the nonmodified organism in the environment of the test site, including any adverse effects on other organisms.

2. Evaluation of whether or not the specific genetic modification (e.g., deletion, insertion, modification of specific DNA sequences) would alter the potential for significant adverse effects.

3. Evaluation of results of tests conducted in contained environments to predict the ecological behavior of the modified organism relative to that of its nonmodified parent.

B. The Nature of the Test

Discuss the following specific features of the experiment that are designed to minimize potential adverse effects of the modified organism:

1. Test site location and area.

2. Introduction protocols.

3. Numbers of organisms and their expected reproductive capacity.

4. Emergency procedures for aborting the experiment.

5. Procedures conducted at the termination of the experiment.

1201

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

RECOMBINANT DNA RESEARCH: REQUEST FOR PUBLIC COMMENT ON "POINTS TO CONSIDER IN THE DESIGN AND SUBMISSION OF HUMAN SOMATIC-CELL GENE THERAPY PROTOCOLS"

AGENCY:

National Institutes of Health, PHS, DHHS.

ACTION:

Request for public comment.

SUMMARY:

This notice publishes for public comment "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols" which was prepared by Working Group on Human Gene Therapy of the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC).

Date:

Comments must be received by (insert date 30 days after the date of publication in the Federal Register).

Address:

Written comments and recommendations should be submitted to the Director, Office of Recombinant DNA Activities, Building 31, Room 3B10, National Institutes of Health, Bethesda, Maryland 20205. All comments received in timely response to this notice will be considered and will be available for public inspection in the above office on weekdays between the hours of 8:30 a.m. and 5:00 p.m.

FOR FURTHER INFORMATION CONTACT:

Background information can be obtained from Dr. William J. Gartland, Office of Recombinant DNA Activities, Building 31, Room 3B10, National Institutes of Health, Bethesda, Maryland 20205 (301) 496-6051.

SUPPLEMENTARY INFORMATION:

Background

At its April 11, 1983, meeting, the NIH Recombinant DNA Advisory Committee (RAC) endorsed a proposal to form a working group to comment and report to RAC on the "Report on the Social and Ethical Issues of Genetic Engineering with Human Beings" issued by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. The President's Commission began its study in September 1980 in response to a request of the President's Science Advisor. Concern had been expressed earlier that year by the nation's three major religious associations that no governmental body was "exercising adequate oversight or control, nor addressing the fundamental ethical questions in a major way." The Commission's report, issued in November 1982, concluded that continuing oversight of the field is desirable and suggested that one possible oversight mechanism could be revising RAC's responsibilities.

The RAC Working Group for Development of Response to President's Commission's Report on Social and Ethical Issues met at the NIH on June 24, 1983, and prepared a proposal for consideration by the full RAC at its September 19, 1983, meeting.

The working group's primary recommendations were that:

1. The membership of the RAC be modified to include adequate representation to deal credibly with these issues.

2. Procedures should be developed for the coordinate consideration of experiments involving the use of recombinant DNA technology in humans by the Institutional Review Boards (IRBs), the Office for Protection from Research Risks (OPRR), the Food and Drug Administration (FDA), the Institutional Biosafety Committees (IBCs), the Office of Recombinant DNA Activities (ORDA), and the Recombinant DNA Advisory Committee (RAC).

3. The NIH Guidelines for Research Involving Recombinant DNA Molecules should be reviewed for their adequacy and clarity in dealing with human experimentation.

The RAC discussed this proposal at its September 19, 1983, meeting. It was noted that the recommendations were based on several premises. These are: (1) there is currently no other national body that deals with ethical issues in the biomedical field; (2) RAC's expertise would be supplemented by adding experts in the ethical issues of using human subjects; and (3) RAC would review proposals on a case-by-case basis in response to investigator-initiated research. RAC's review would supplement review by IBCs and IRBs.

The RAC unanimously accepted the working group's recommendations. The RAC Working Group on Social and Ethical Issues (formerly called the RAC Working Group for Development of Response to President's Commissions' Report on Social and Ethical Issues) met at the NIH on December 13, 1983. The working group requested that the following modifications to the Guidelines be published for comment and be considered by the RAC at its February 1984 meeting.

1. A new Section III-A-4 would be added to Section III-A, Experiments that Require RAC Review and NIH and IBC Approval Before Initiation, of the NIH Guidelines for Research Involving Recombinant DNA Molecules:

   "III-A-4. Deliberate transfer of recombinant DNA or DNA derived from recombinant DNA into human subjects. The requirement for RAC review should not be considered to preempt any other required review of experiments with human subjects. IRB review of the proposal should be completed before submission to NIH."

2. Section III-B-4-b of Section III-B-4, Recombinant DNA Experiments Involving Whole Animals or Plants, would be footnoted. Section III-B-4-b reads as follows:

   "III-B-4-b. For all experiments involving whole animals and plants and not covered by III-B-4-a, the appropriate containment will be determined by the IBC."

3. A footnote concerning Section III-B-4-b of Section III-B-4, Recombinant DNA Experiments Involving Whole Animals or Plants would be added to Section V, Footnotes and References of Sections I-IV, as follows:

   "For recombinant DNA experiments involving human subjects, see Section III-A-4."

In addition, the Working Group on Social and Ethical Issues suggested that a working group composed of 9 members (including Chair) be formed to conduct initial review of proposals for experiments involving human subjects submitted to the RAC. Individuals with expertise in basic science, clinical medicine,

law, and ethics would be appointed to the working group. Liaison members from the Food and Drug Administration and the Office for Protection from Research Risks would also be appointed. The working group might use as resource material reports such as "Splicing Life" prepared by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.

The working group proposal was published in the January 5, 1984, Federal Register (49 FR 696). No comments were received during the comment period.

The RAC discussed this proposal at its February 6, 1984, meeting. It was pointed out that the phrase "or DNA derived from recombinant DNA" was included in the proposed Section III-A-4 to keep coverage under this Section of the Guidelines even if the DNA to be introduced into the human subject is first cleaved from the vector and, therefore, no longer "recombinant DNA."

By a vote of fifteen in favor, none opposed, and two abstentions, the RAC recommended that the changes in the Guidelines proposed by the working group and published in the January 5, 1984, Federal Register be accepted.

This recommendation was accepted by the Director, NIAID, in a notice published in the April 25, 1984, Federal Register (49 FR 17844). However, concerns were raised about the intended scope of the new Section III-A-4; e.g., would this language be construed to cover feeding of bacteria containing recombinant DNA or the administration of vaccines containing recombinant DNA to human subjects. On checking with members of the Working Group on Social and Ethical Issues, the Director, NIAID, verified that it was their intent to include under Section III-A-4 only experiments in which the intent is to modify stably the genome of

cells of a human subject and not experiments involving feeding of bacteria containing recombinant DNA or the administration of vaccines containing recombinant DNA. The following clarifying footnote was, therefore, added to Section III-A-4:

> "Section III-A-4 only covers those experiments in which the intent is to modify stably the genome of cells of a human subject. Other experiments involving recombinant DNA in human subjects such as feeding of bacteria containing recombinant DNA or the administration of vaccines containing recombinant DNA are not covered in Section III-A-4 of the Guidelines."

In addition, appropriate clarifying language was added to the new footnote concerning Section III-B-4-b.

The RAC Working Group on Human Gene Therapy held its first meeting (open to the public) on October 12, 1984. At the October 29, 1984, RAC meeting, the Chair of the working group presented a progress report and a draft outline of the Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols. At a second meeting (open to the public) held on November 16, 1984, the working group further refined the document that follows. The draft that emerged from the November 16 meeting was circulated to all members of the RAC and the working group for comments, and numerous suggested changes were incorporated into the document.

The Working Group on Human Gene Therapy is comprised of three laboratory scientists, three clinicians, three ethicists, three lawyers, two specialists in public policy, and a representative of the public. The group is assisted by an executive secretary, three liaison members, and a consultant. The names and institutional affiliations of these persons follow:

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Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols

The following "Points to Consider" document prepared by the RAC Working Group on Human Gene Therapy is now published for public comment and is being sent to all Institutional Review Boards (IRB) for comment. Comments received will be circulated to all RAC and working group members. The working group will then meet to review the public comments. The "Points to Consider" document and the public comments received will be considered at the next RAC meeting.

POINTS TO CONSIDER IN THE DESIGN AND SUBMISSION OF HUMAN SOMATIC-CELL GENE THERAPY PROTOCOLS

WORKING GROUP ON HUMAN GENE THERAPY
NIH RECOMBINANT DNA ADVISORY COMMITTEE

OUTLINE

Introduction

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B. Research design, anticipated risks and benefits

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3. Clinical procedures, including patient monitoring

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C. Other concerns of society

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A. Original protocol

B. IRB and IBC minutes and recommendations

C. One-page abstract of gene therapy protocol

D. Curricula vitae for professional personnel

E. Responses to the questions raised in these "Points to Consider"

F. Indication of other federal agencies to which the protocol is being submitted

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POINTS TO CONSIDER IN THE DESIGN AND SUBMISSION OF HUMAN SOMATIC-CELL GENE THERAPY PROTOCOLS

Introduction

Experiments in which recombinant DNA[1] is introduced into cells of a human subject with the intent of stably modifying the subject's genome are covered by Section III-A-4 of the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules (49 FR 46266). Section III-A-4 requires such experiments to be reviewed by the NIH Recombinant DNA Advisory Committee (RAC) and approved by the NIH. RAC consideration of each proposal will follow publication of a precis of the proposal in the Federal Register, an opportunity for public comment, and review of the proposal by a working group of the RAC. RAC recommendations on each proposal will be forwarded to the NIH Director for a decision, which will then be published in the Federal Register. In accordance with Section IV-C-1-b of the NIH Guidelines, the NIH Director may approve proposals only if he finds that they present "no significant risk to health or the environment."

In general, it is expected that somatic-cell gene therapy protocols will not present a risk to the environment as the recombinant DNA is expected to be confined to the human subject. Nevertheless, item I-B-4-b of the "Points to Consider" document asks the researchers to address specifically this point.

[1]Experiments using retroviruses (RNA) as vectors are also covered by the NIH Guidelines for Research Involving Recombinant DNA Molecules and hence by this document. Section III-A-4 applies to both recombinant DNA and DNA derived from recombinant DNA.

This document is intended to provide guidance in preparing proposals for NIH consideration under Section III-A-4. Not every point mentioned in the document will necessarily require attention in every proposal. It is expected that the document will be considered for revision at least annually as experience in evaluating proposals accumulates.

A proposal will be considered by the RAC only after the protocol has been approved by the local Institutional Biosafety Committee (IBC) and by the local Institutional Review Board (IRB) in accordance with Department of Health and Human Services regulations for the protection of human subjects (45 CFR, Part 46). If a proposal involves children, special attention should be paid to Subpart D of these regulations. The IRB and IBC may, at their discretion, condition their approval on further specific deliberation by the RAC and its working group. Consideration of gene therapy proposals by the RAC may proceed simultaneously with review by any other involved federal agencies (e.g., the Food and Drug Administration) provided that the RAC is notified of the simultaneous review. The committee expects that the first proposals submitted for RAC review will contain no proprietary information or trade secrets; therefore, the review will be open to the public. The public review of these protocols will serve to educate the public not only on the technical aspects of the proposals but also on the meaning and significance of the research.

The clinical application of recombinant DNA techniques to human gene therapy raises two general kinds of questions. Part I of this document deals with the short-term risks and benefits of the proposed research to the patient[2] and to

[2] The term "patient" and its variants are used in the text as a shorthand designation for "patient-subject."

other people as well as with issues of equity in the selection of subjects, informed consent, and privacy and confidentiality. In Part II, investigators are requested to address broader ethical and social issues pertaining to the research and its longer-term implications. These broader questions go beyond the usual purview of IRBs and reflect the kinds of public concerns discussed by a recent presidential commission in its report entitled Splicing Life: The Social and Ethical Issues of Genetic Engineering with Human Beings. Responses to the questions raised in these "Points to Consider" should be in the form of either written answers or references to specific sections of the protocol or other documentation which accompanies the proposal. In addition, Part III of the "Points to Consider" summarizes other documentation that will assist the RAC and its working group in their review of gene therapy proposals.

I. Description of Proposal

A. Objectives and rationale of the proposed research

State concisely the overall objectives and rationale of the proposed study. Please provide information on the following specific points:

1. Why is the disease selected for treatment by means of gene therapy a good candidate for such treatment?

2. Describe the natural history and range of expression of the disease selected for treatment. In your view, are the usual effects of the disease predictable enough to allow for meaningful assessment of the results of gene therapy?

3. Is the protocol designed to prevent all manifestations of the disease, to halt the progression of the disease after symptoms have begun to appear, or to reverse manifestations of the disease in seriously ill victims?

4. What alternative therapies exist? In what groups of patients are these therapies effective? What are their relative advantages and disadvantages as compared with the proposed gene therapy?

B. Research design, anticipated risks and benefits

1. Structure and characteristics of the biological system

Provide a full description of the methods and reagents to be employed for gene delivery and the rationale for their use. The following are specific points to be addressed:

a. What is the structure of the cloned DNA that will be used?

(1) Describe the gene (genomic or cDNA), the bacterial plasmid or phage vector, and the delivery vector (if any). Provide complete sequence analysis or a detailed restriction map of the total construct.

(2) What regulatory elements does the construct contain (e.g., promoters, enhancers, polyadenylation sites, replication origins, etc.)?

(3) Describe the steps used to derive the DNA construct.

b. What is the structure of the material that will be administered to the patient?

(1) Describe the preparation and structure of all materials that will be given to the patient or used to treat the patient's cells.

(a) If DNA, what is the purity (both in terms of being a single DNA species and in terms of other contaminants)? What tests have been used and what is the sensitivity of the tests?

(b) If a virus, how is it prepared from the DNA construct? In what cell is the virus grown (any special features)? What medium and serum are used? How is the virus purified? What is its structure and purity? What steps are being taken (and assays used with their sensitivity) to detect and eliminate any contaminating materials (DNA, proteins, etc.) or contaminating viruses or other organisms in the cells or serum?

(2) Describe any other material to be used in preparation of the material to be administered to the patient. For example, if a viral vector is proposed, what is the nature of the helper virus or cell line? If carrier particles are to be used, what is the nature of these?

2. Preclinical studies, including risk-assessment studies

Describe the experimental basis (derived from tests in cultured cells and laboratory animals) for claims about the efficacy and safety of the proposed system for gene delivery.

a. Laboratory studies of the delivery system

(1) What cells are the intended recipients of gene therapy? If recipient cells are to be treated in vitro and returned to the patient, how will the cells be characterized before and after treatment? What is the theoretical and practical basis for assuming that only the treated cells will act as recipients?

(2) Is the delivery system efficient in the sense that it results in the insertion of the desired unrearranged DNA sequences into an adequate number of the patient's cells?

(3) How is the structure of the added DNA sequences monitored and what is the sensitivity of the analysis? Is the added DNA extrachromosomal or integrated?

(4) How many copies are inserted per cell? How stable is the inserted DNA both in terms of its continued presence and its structural stability?

b. Laboratory studies of gene expression

Is the inserted gene expressed? To what extent is expression only from the desired gene (and not from the surrounding DNA)?

In what percentage of cells does expression occur? Is the product biologically active? What percentage of normal activity results from the inserted gene? Is the gene expressed in cells other than the target cells? If so, to what extent?

c. Laboratory studies pertaining to the safety of the delivery/ expression system

(1) If a retroviral system is used:

(a) What cell types have been infected with the retroviral vector preparation? Which cells, if any, produce infectious particles?

(b) How stable are the retroviral vector and the resulting provirus against loss, rearrangement, recombination, or mutation? What information is available on how much rearrangement or recombination with endogenous or other viral sequences is likely to occur in the patient's cells? What steps have been taken in designing the vector to minimize instability or variation? What laboratory studies have been performed to check for stability, and what is the sensitivity of the analyses?

(c) What laboratory evidence is available concerning potential harmful effects of the treatment, e.g., malignancy, harmful mutations, regeneration of infectious particles, or immune responses? What steps have been taken in

designing the vector to minimize pathogenicity? What laboratory studies have been performed to check for pathogenicity, and what is the sensitivity of the analyses?

(d) Is there evidence from animal studies that vector DNA has entered untreated cells or specifically germline cells? What is the sensitivity of the analyses?

(e) Has a protocol similar to the one proposed for a clinical trial been carried out in non-human primates and with what results? Specifically, is there any evidence that the retroviral vector has recombined with any endogenous or other viral sequences in the animals?

(2) If a non-retroviral delivery system is used: What animal studies have been done to determine if there are pathological or other undesirable consequences of the protocol (including insertion of DNA into cells other than those treated)? What tests have been used and what is their sensitivity?

3. Clinical procedures, including patient monitoring

Describe the treatment that will be administered to patients and the diagnostic methods that will be used to monitor the success or failure of the treatment.

a. Will cells (e.g., bone marrow cells) be removed from patients and treated in vitro in preparation for gene therapy? If so,

what kinds of cells will be removed from the patients, how many, how often, and at what intervals?

b. Will patients be treated to eliminate or reduce the number of cells containing malfunctioning genes (e.g., through radiation or chemotherapy) prior to gene therapy?

c. What treated cells (or vector/DNA combination) will be given to patients in the attempt to administer gene therapy? How will the treated cells be administered? What volume of cells will be used? Will there be single or multiple treatments? If so, over what period of time?

d. What are the clinical endpoints of the study? How will patients be monitored to assess specific effects of the treatment on the disease? What is the sensitivity of the analyses? How frequently will follow-up studies be done? How long will patient follow-up continue?

e. What are the major potential beneficial and adverse effects of treatment that you anticipate? What measures will be taken in an attempt to control or reverse these adverse effects if they occur? Compare the probability and magnitude of potential adverse effects on patients with the probability and magnitude of deleterious consequences from the disease if gene therapy is not performed.

f. Serious adverse effects of treatment should be reported immediately to both your local IRB and the NIH Office for Protection from Research Risks (phone: 301-496-7005).

g. Reports regarding the general progress of patients should be filed at six-month intervals with both your local IRB and the NIH Office of Recombinant DNA Activities (phone: 301-496-6051). These twice-yearly reports should continue for a sufficient period of time to allow observation of all major effects (at least three to five years).

h. If a treated patient dies, will an autopsy be requested? If so, please indicate what special studies, if any, will be performed.

4. Public health considerations

Describe the potential benefits and hazards of the proposed therapy to persons other than the patients being treated.

a. What potential benefits or hazards are postulated?

b. Is there any expectation that the recombinant DNA will spread from the patient to others or to the environment?

c. What precautions will be taken, if any, to protect others (e.g., patients sharing a room, health-care workers, or family members) from such potential hazards?

5. Qualifications of investigators, adequacy of laboratory and clinical facilities

Indicate the relevant training and experience of the personnel who will be involved in the preclinical studies and clinical administration of gene therapy. In addition, please describe the laboratory and clinical facilities where the proposed study will be performed.

a. What professional personnel (medical and nonmedical) will be involved in the proposed study? What are their specific qualifications and experience with respect to the disease to be treated and with respect to the techniques employed in molecular biology? Please provide curricula vitae.

b. At what hospital or clinic will the treatment be given? Which facilities of the hospital or clinic will be especially important for the proposed study? Will patients occupy regular hospital beds or clinical research center beds?

C. Selection of subjects

Estimate the number of patients to be involved in the proposed study of gene therapy. Describe recruitment procedures and patient eligibility requirements. Indicate how equity consideration in the selection of subjects will be handled.

1. How many patients do you plan to involve in the proposed study?

2. How many eligible patients do you anticipate being able to identify each year?

3. What recruitment procedures do you plan to use?

4. What selection criteria do you plan to employ? What are the exclusion and inclusion criteria for the study?

5. What equity issues, if any, are likely to arise in the selection of patients? How will these issues be addressed?

D. Informed consent

Indicate how patients will be informed about the proposed study and how their consent will be solicited. If the study involves pediatric or mentally handicapped patients, describe procedures for seeking the permission of parents or guardians and, where applicable, the assent of each patient. Areas of special concern include potential adverse effects, financial costs, privacy, and the right to withdraw from further participation in the study.

1. Will the major points covered in IA-IC of this document be disclosed to potential participants in this study and/or parents or guardians in language that is understandable to them? (Include a copy of the patient consent form as part of the documentation requested in Part III below.)

2. Will the innovative character and the theoretically-possible adverse effects of gene therapy be discussed with patients and/or parents or guardians? Will the potential adverse effects be compared with the consequences of the disease? What will be said to convey that some of these adverse effects, if they occur, could be irreversible?

3. Will the financial costs of gene therapy and any available alternative therapies be explained to patients and/or parents or guardians?

4. Will patients and/or their parents or guardians be informed that the innovative character of gene therapy may lead to great interest by the media in the research and in treated patients? What special procedures, if any, will be followed to protect the privacy of patients and their families?

5. Will patients and/or their parents or guardians be informed of their right to withdraw at any time from the proposed study and of the consequences of withdrawal at the various stages of the experiment? State the extent to which subjects will be specifically advised on the reversibility or irreversibility of procedures that are performed during the course of the experiment.

E. Privacy and confidentiality

Indicate what measures will be taken to protect the privacy of gene therapy patients and their families as well as to maintain the confidentiality of research data.

1. What provisions will be made to honor the wishes of individual patients (and the parents or guardians of pediatric or mentally handicapped patients) as to whether, when, or how the identity of patients is publicly disclosed?

2. What provision will be made to maintain the confidentiality of research data, at least in cases where data could be linked to individual patients?

II. Social Issues

The following issues are beyond the normal purview of local IRBs. However, since these issues have arisen in public debates about human gene therapy and the potential future applications of genetic techniques, the RAC and its working group request that investigators respond to questions A and B below and discuss, at their discretion, the general issues enumerated in point C.

A. What steps will be taken to ensure that accurate information is made available to the public with respect to such public concerns as may arise from the proposed study?

B. Do you or your funding sources intend to protect under patent or trade secret laws either the products or the procedures developed in the proposed study? If so, what steps will be taken to permit as full communication as possible among investigators and clinicians concerning research methods and results?

C. The following issues will also be considered by the RAC and its working group in reviewing each gene therapy proposal:

1. How strong is the evidence that the proposed somatic-cell gene therapy will not affect the reproductive cells of patients?

2. Is the proposed somatic-cell gene therapy an extension of existing methods of health care, or does it represent a distinct departure from present treatments of disease?

3. Is it likely that somatic-cell therapy for human genetic disease will lead to: (a) germ-line gene therapy, (b) the enhancement of human capabilities through genetic means, or (c) eugenic programs encouraged or even mandated by governments?

III. REQUESTED DOCUMENTATION

In addition to responses to the questions raised in these "Points to Consider," please submit the following materials:

A. Your protocol (including consent form) as approved by your local IRB and IBC.

B. Local IRB and IBC minutes and recommendations that pertain to your protocol.

C. A one-page abstract of the gene therapy protocol.

D. Curricula vitae for professional personnel.

E. An indication of other federal agencies to which the protocol is being submitted for review.

F. Any other material which you believe will aid in the review.

G. Other pertinent material.

Dated: January 11, 1985

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OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every federal research program in which DNA recombinant molecule techniques could be used, it has been determined to be not cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every

federal program would be included as many federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.